for treating malignant cancer cell lines (such as those listed in Table 1 of the present application), the specification is allegedly non-enabling for a method for preventing or treating malignant or benign neoplasms as presently claimed.

The rejection is traversed.

Attention is drawn to the present application a page 4, line 35 to page 5, line 31, wherein the topical application of an active enamel substance to a suitable surface at or on affected tissue is clearly described. Such description is provided in sufficient detail to render a person skilled in the art able to practice and implement such treatment commensurate in scope with the claimed invention without undue experimentation.

Additionally, the Office Action implies that the specification is allegedly deficient in that there is no evidence presented as to the treatment of "normal" cell line counterparts. The Office Action goes on to assert that the scientific basis of an experiment is the testing and observation of results between a set of normal samples versus diseased samples.

While such a theory may be generally applicable for a certain category of experimental procedures or analyses, it should be emphasized that all experiments are not alike. Indeed, there is no such thing as a single suitable design or set-up for any given scientific experiment. On the contrary, the overall design of each experiment is necessarily adjusted to address the particular technical problem to be investigated. That must be determined on an experiment to experiment basis.

In the present invention, the experiments were performed to investigate whether or not active enamel substances could reduce epithelial cancer cell growth. It has been shown that active enamel substances do not reduce but rather stimulate growth of "normal" cells, e.g., untransformed fibroblasts. (See, e.g., Gestrelius et al., 1997, *J. Clinical Periodontology*, Vol. 24, 685-692, a copy of which is enclosed along with a Supplemental Information Disclosure Statement/PTO 1449 form.)

Thus, the controls chosen in the present application were untreated HeLa cells versus treated HeLa cells (see the present application at page 23, lines 17-18). Moreover, the present invention addresses the technical problem of the risk of transformed cells migrating from the site of a removed epithelially derived tumor or neoplastic tissue and the recurrence of said tumor or neoplastic tissue after surgery (see the present application at page 5, lines 16-27). As described above, the active enamel substance of the invention will drastically reduce the risk of migration or recurrence of the removed epithelially derived tumor or neoplasm when administered topically. Indeed, this is testament to the present invention's surprising capability of selectively reducing the growth of epithelially derived cancer cells.

Further, the Office Action raises the question of how an active substance could discriminatorily induce apoptosis in a neoplasm versus a non-transformed cell. It is respectfully submitted, however, that parameters such as the different turnover rate and metabolism in transformed versus non-transformed cells are well established. Clearly, the topical application of active enamel substances of the invention (described in detail in the present application at page 14, line 21 to page 20, line 10) will lead to the transformed cells incorporating a much higher dosage of active enamel substance than the "normal" cells that are not proliferating at the same rate.

In support of the aforementioned arguments, Applicants enclose herewith certain data that confirms the proposition that "normal" epithelial control cells are not significantly affected by active enamel substances (See Lyngstadaas et al., 2001. *J. Clinical Periodontology*, Vol. 28, pages 181-188, a copy of which is enclosed and cited in the concurrently filed Supplemental Information Disclosure Statement/PTO 1449 form.)

Further, while Applicants believe that the full scope of the claims are indeed enabled by the specification, in order to expedite prosecution of the application, claim 28 has been amended to include only topical treatment of epithelially derived malignant or benign neoplasms.

In view of the arguments set forth above and the within amendments, reconsideration and withdrawal of the enablement rejection are thus requested.

Claims 28-31 and 32-46 stand rejected under 35 USC §112, second paragraph, on the grounds that such claims are allegedly rendered vague and indefinite due to their use of several objectionable terms.

The rejection is traversed.

Applicants submit that the noted claims are abundantly clear and definite when read in view of the supporting specification, as is proper.

For example, the Office Action objects to the use of the term "...therapeutically effective amount of an active enamel substance" in claim 28. Attention is drawn to the present application at page 19, line 23, to page 20, line 2, for its discussion of concentration of the active enamel substance in the pharmaceutical use context. In particular, it is indicated that the concentration of the active enamel substance depends on a variety of different parameters, and given the disclosure of the present application, it is submitted that a person skilled in the art could readily select the relevant concentration according to established guidelines as cited in the specification.

Further, the Office Action objects to use of the term "affected tissue" as it appears in claim 29. Attention is directed to the present application at page 4, line 37 to page 5 line 14, where that term is clearly defined, e.g., as tissue comprising a significant portion of epithelial cells, such as skin or mucosal tissue, glandular tissues, bone and muscle tissue. In this context, as is well understood by a person skilled in the art, an affected tissue is a tissue that is transformed from a normal tissue to a neoplastic tissue.

Similarly, the Office Action objects to "active enamel substance" as it appears in claim claims 28-41 and 43. It is respectfully submitted that such term is clearly defined in the present

application at page 1, lines 28-30, as a collective term for enamel matrix, enamel matrix derivatives and/or enamel matrix proteins.

Still further, the Office Action objects to use of the terms "derivatives", "derivatives thereof" and "mixtures thereof" in the context of enamel matrix derivates and mixtures. Applicants submit that the disclosure at page 7, lines 21-27 clearly describes derivatives and mixtures of the group consisting of enamelins, amelogenins, non-amelogenins, proline-rich non-amelogenins, amelins, tuftelins. As such, the noted claims are indeed quite clear when read in light of the supporting specification.

Reconsideration and withdrawal of the rejection are requested.

It is believed the application is in condition for immediate allowance, which action is earnestly solicited.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES TO CLAIMS

(Additions are underlined and deletions are bracketed.)

Claim 28 is amended as follows:

28. (Twice amended) A method for treating of epithelially derived malignant or benign neoplasms, the method comprising administering topically to a mammal in need thereof a therapeutically effective amount of an active enamel substance.